Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 36, 37, 40, 41, 43, 44 and 46-49 are pending in the application, with claim 36 being the independent claim.

Claim 39 has been canceled without prejudice or disclaimer. Claim 36 has been amended to recite "separin." No new matter has been added by these amendments.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under 35 U.S.C. § 112, 1st Paragraph

In the Office Action at page 2, sections 3-4, the Examiner rejected claims 36, 37, 39-41, 44, and 46-49 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

Amended claim 36 recites "[a] method for identifying compounds that have the activity of inhibiting sister chromatid separation in eukaryotic cells, comprising: (a) incubating with a test compound a *separin*, in the presence of a substrate for its proteolytic activity; (b) determining the inhibiting effect of the test compound on the proteolytic activity of the *separin*" (emphasis added).

According to the specification at page 4, line 3, "[b]oth the dissociation of Scc1p from chromosomes and the separation of sister chromatids are dependant on a specialized sister

separating protein (a separin) called Esp1 (Ciosk et al., 1998)." In addition to the disclosure of Esp1 and human separin, the specification also discloses, at page 4, lines 5-9, that "[s]eparin homologous to Esp1 exist in the fission yeast Schizosaccharomyces pombe, in the fungus Aspergillus nidulans, in the nematode worm Caenorhabditis elegans, the fruit fly Drosophila melanogaster, in the frog Xenopus laevis, in the plant Arabidopsis thaliana, and in man." The specification further states, at page 17, lines 19-21, that "the term 'separin' is used as a synonym for any cysteine endopeptidase with separin-like activity, including the yeast homolog Espl."

Applicants have shown that Esp1 promotes the cleavage of Scc1p and its dissociation from chromosomes both in vitro and in vivo. See specification at page 6, line 24, through page 7, line12. Applicants have further demonstrated that: "[i]nspection of the amino acid sequence within the evolutionary conserved C-terminal half of Esp1 revealed that exactly one cysteine and one histidine residue are conserved in all known separin homologues. These two residues might therefore form the catalytic dyad of a new subclass of cysteine protease." See specification at page 10, lines 17-21. Furthermore, studies showed that N-ethyl maleimide, an inhibitor specific for proteases using a catalytic cysteine residue, inhibit the cleavage activity of Esp1 on Scc1. See specification at page10, lines 15-17. In addition, Applicants have also shown that a mutant Esp1, containing mutations of both the cysteine and histidine residues to alanine, completely abolished the proteolytic activity of Esp1 on Scc1. See specification at page 11, lines 1-9. Applicants have also shown a structure/activity relationship for Esp1:

> When the amino acid sequences surrounding the potential catalytic dyad were further analyzed, it was found that both the cysteine and the histidine residues are preceded by a sequence

> stretch predicted to form a hydrophobic beta sheet. Furthermore, the histidine is invariably flanked by two glycine residues and the cysteine is preceded by a glycine providing the possibility for a tight turns before or after the catalytic residues. This arrangement of histidine and a cysteine catalytic dyad residues fixed at the ends of two neighbouring strands of hydrophobic beta sheet is used in the caspase family of proteases and it seems likely that the same arrangement is used in separins like Esp1.

See specification at page 10, lines 21-30.

In view of the above, it is clear that the inventors had possession of the claimed invention at the time the application was filed and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections Under 35 U.S.C. § 112, 2nd Paragraph

In the Office Action at page 3, sections 5-7, claims 36, 37, 39-41, and 44-49 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection.

The Examiner asserted that the phrase "separin-like endopeptidase activity" renders claim 36 (and the claims depending therefrom, claims 37, 39-41 and 44-49) "vague and indefinite because the meaning of the phrase is not known" (see Office Action at page 3, section 7).

Claim 36 has been amended to recite "a separin." The term is neither vague nor indefinite because a person of ordinary skill in the art, aided by the specification as explained above, would be able to identify and use a separin in the claimed invention.

The phrase "co-factor of said protease" in claim 39 (reference to claim 29 in the Office Action is believed to be a typo) was alleged to be vague and indefinite. Claim 39 has been canceled without prejudice or disclaimer.

The phrase "fragment or variant thereof" in claims 45 and 46 and the phrase "cleavable fragment or variant thereof" in claim 47 were alleged to be vague and indefinite because the specific sequences/structures are not known. Applicants respectfully traverse this rejection.

Claim 45 is not currently pending. Claim 46 is directed to a method of identifying a compound that has the activity of inhibiting sister chromatid separation in eukaryotic cells by incubating a test compound with a separin in the presence of a substrate that is human SCC1 or a fragment or variant thereof. Human SCC1 was known. An assay for detecting whether a fragment or variant of SSC1 has the activity of a separin is provided in the specification, for example, at page 5, line 30, through page 6, line 3, and in Example 2 at page 34. Furthermore, the specification discloses a "fragment" of SCC1 as "the peptide derived from human SCC1" (see specification at page 24, lines 11-14). The specification also discusses "variants" and states that "variants can be generated either by synthesizing variant peptides or by mutating DNA sequences from genes encoding cohesion proteins" (see specification at page 20, lines 1-2).

Claim 47 depends from claim 46 and further recites that the substrate is a polypeptide with the amino acid sequence of SEQ ID NO:1, or a cleavable fragment or variant thereof. The specification points out that "when designing a peptide substrate . . . it has to be tested whether the substrate is efficiently cleaved by separin" (see specification at page 20, lines 17-19). This is because the method of the present invention tests the inhibiting effect of a test compound on a separin in the presence of *a substrate for its proteolytic activity.* The

specification, for example, at page 5, line 30, through page 6, line 3, and in Example 2 at page 34, provides an assay for identifying a cleavable fragment or variant thereof of SCC1.

In view of the above, the phrases in claims 46 and 47 are not vague and indefinite and it is respectfully requested that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claim 39 has been cancelled without prejudice or disclaimer.

36. (once amended) A method for identifying compounds that have the activity of inhibiting sister chromatid separation in eukaryotic cells, comprising:

(a) incubating with a test compound a separin [protease, which has separin-like cysteine endopeptidase activity,] in the presence of a substrate for its proteolytic activity; and

(b) determining the inhibiting effect of the test compound on the proteolytic activity of the separin [protease].